

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of claims:**

Claim 1 (withdrawn): A non-human transgenic animal whose germ cells and somatic cells contain a knockout mutation in DNA encoding 4E-BP1, and wherein said transgenic animal shows a phenotype of an altered glucose and/or fat metabolism as compared to a control animal.

Claims 2 (withdrawn) : The transgenic animal of claim 1, wherein said animal is a mammal.

Claim 3 (withdrawn): The mammal of claim 2, wherein said mammal is a mouse.

Claim 4 (withdrawn): A cell line derived from the non-human transgenic animal of claim 1.

Claim 5 (withdrawn): A cell line derived from the mouse of claim 3.

Claim 6 (withdrawn): A method of producing a non-human transgenic animal, in which at least some cells thereof contain an altered gene encoding an altered 4E-BP1, said altered gene having been targeted to disrupt the wild type 4E-BP1 gene in said transgenic animal, said method comprising:

- a) providing an altered gene encoding the altered form of 4E-BP1 and designed to target and disrupt said wild type 4E-BP1 gene of an embryonic stem cells (ES) of said animal;
- b) introducing said altered gene in said ES cells;
- c) selecting ES cells in which said altered 4E-BP1 gene has disrupted said wild type 4E-BP1 gene;
- d) injecting said selected ES cells of c) into blastocysts;
- e) implanting said blastocysts of d) in a pseudopregnant animal; and
- f) producing a transgenic animal having at least some cells having said altered 4E-BP1 gene encoding said altered 4E-P1.

Claim 7 (original): A method of identifying an agent which modulates glucose or fat metabolism in vivo comprising:

- a) administering an agent suspected of being a modulator of cap-dependent translation in an animal;
- b) measuring glucose and/or lipid levels in the animal of step a) and comparing same with that of a control animal, not having been administered said agent, wherein a difference in glucose and/or lipid levels of the animal of step a) as compared to that of the control animal identifies said agent as a modulator of glucose or fat metabolism in vivo.

Claim 8 (original): The method of claim 7, wherein said positive modulator of cap-dependent translation is a modulator of the level or of the activity of 4E-BP1.

Claim 9 (original): The method of claim 8, wherein said agent increases and/or strengthens the interaction of 4E-BP1 with eIF-4E.

Claim 10 (original): The method of claim 7, wherein said agent decreases and/or weakens the interaction of 4E-BP1 with eIF-4E.

Claim 11 (original): The method of claim 7, wherein said agent decreases the amount of eIF-4F pre-initiation complex, thereby decreasing the translation of mRNAs implicated in glucose or lipid metabolism.

Claim 12 (original): The method of claim 11, wherein said decrease in the amount of eIF-4F pre-initiation complex involves a sequestration of eIF-4E in a complex with an eIF-4E sequestering agent.

Claim 13 (currently amended): The method of claim 12, wherein said eIF-4E sequestering agent comprises a sequence having an amino acid sequence selected from YxxxxL $\phi$  (SEQ ID NO: 21), Yx+xf $\phi\phi$  (SEQ ID NO: 28), + $\phi$ xxYx+xf $\phi\phi$  (SEQ ID NO: 22), + $\phi\phi$ Y-+xF/A $\phi\phi$ xxRxSP (SEQ ID NO: 23), and + $\phi\phi$ Y-+xfL $\phi$ xxRxSP (SEQ ID NO: 24), or + $\phi$ xYx+xfL $\phi$ xxxxxx (SEQ ID NO: 26) wherein + and - refer to a charged amino acid;  $\phi$  is a hydrophobic amino acid; x is any amino acid; and the capital letters refer to the known one letter code for amino acids.

Claim 14 (original): The method of claim 13, wherein said sequestering agent is selected from 4E-BP, eIF4G, p82, p150, p130 and p20.

Claim 15 (original): The method of claim 14, wherein said sequestering agent is selected from 4E-BP1, 4E-BP2, 4E-BP3, eIF-4G1, eIF4-G2, 4E-BP, and eIF-4G.

Claim 16 (original): The method of claim 15, wherein said sequestering agent is selected from 4E-BP1, 4E-BP2, 4E-BP3, eIF-4G1, eIF-4G2, 4E-BP, and eIF-4G.

Claim 17 (previously presented): A method of identifying an agent which modulates glucose and/or fat metabolism *in vivo* comprising:

- a) providing a translationally active preparation of translation factors and at least one mRNA having a cap structure whose translation is cap-dependent;
- b) measuring the initiation of translation on said mRNA, or the binding of at least some translation factors of a) to said cap of said mRNA in the presence and in the absence of an agent suspected of modulating the translation efficiency of cap-dependent mRNAs or the binding of translation factors to the cap structure thereof, thereby identifying an agent which modulates cap-dependent translation and wherein a difference in the translation activity and/or binding in the presence of the agent, as compared to that in the absence thereof identifies said agent as a modulator of cap-dependent translation;
- c) administering said agent identified in b) to an animal; and
- d) measuring glucose and/or lipid levels in the animal of step c) and comparing same with that of a control animal, not having been administered said agent, wherein a difference in glucose and/or lipid levels of the animal of step c) as compared to that of the control animal identifies said agent as a modulator of glucose or fat metabolism *in vivo*.

Claim 18 (original): The method of claim 17, where the agent is obtained from a library of compounds.

Claim 19 (original): The method of claim 18, wherein the animal is a mammal.

Claim 20 (original): The method of claim 19, wherein said mammal is a mouse or human.

Claim 21 (withdrawn): A modulator of glucose or fat metabolism *in vivo* identified by the method of claim 17.

Claim 22 (withdrawn): A method of decreasing fat tissue growth and/or weight gain, comprising:

a) administering an agent which desequesters eIF-4E from a sequestering agent, thereby increasing the amount of eIF-4E available for a formation of eIF-4F preinitiation complex, leading to an increase of translation of cap-dependent mRNAs implicated in a reduction of a tissue growth and/or weight gain.

Claim 23 (withdrawn): The method of claim 22, wherein said sequestration of eIF-4E is through its interaction with 4E-BP1.

Claim 24 (withdrawn): The method of claim 23, wherein said desequestration of eIF-4E from 4E-BP1 is effected by an antibody specific to the eIF-4E interaction domain of 4E-BP1, or an epitope-bearing portion thereof.

Claim 25 (withdrawn): The method of claim 24, wherein said desequestration or said inhibition of said sequestration is effected by an inhibition of the synthesis of 4E-BP1.

Claim 26 (withdrawn): The method of claim 25, comprising an agent which inhibits the synthesis of 4E-BP1, wherein said agent comprises an antisense RNA complementary to the nucleotide sequence encoding for 4E-BP1.

Claim 27 (withdrawn): A method of determining whether an agent modulates fat tissue growth and/or weight gain in an animal comprising:

a) providing a translationally active preparation of translation factors and at least one mRNA having a cap structure whose translation is cap-dependent;

b) measuring the initiation of translation on said mRNA, or the binding of at least some translation factors of a) to said cap of said mRNA in the presence and in the absence of an agent suspected of modulating the translation efficiency of cap-dependent mRNAs or the binding of translation factors to the cap structure thereof, thereby identifying an agent which modulates cap-dependent translation and wherein a difference in the translation activity and/or binding in the presence of the agent, as compared to that in the absence thereof identifies said agent as a modulator of cap-dependent translation;

c) administering said agent identified in b) to an animal; and  
d) measuring fat tissue growth and/or weight gain in the animal of step c)  
and comparing same with that of a control animal, not having been administered said agent,  
wherein a difference in fat tissue growth and/or weight gain of the animal of step c) as  
compared to that of the control animal identifies said agent as a modulator of fat tissue  
growth and/or weight gain *in vivo*.

Claim 28 (withdrawn): The method of claim 27, where the agent is obtained from a  
library of compounds.

Claim 29 (withdrawn): The method of claim 28, wherein the animal is a mammal.

Claim 30 (withdrawn): The method of claim 29, wherein said mammal is a mouse or  
human.

Claim 31 (withdrawn): A modulator of glucose or fat metabolism *in vivo* identified  
by the method of claim 28.

Claim 32 (withdrawn): A method of treating obesity, comprising administering to an  
obese animal, or an animal susceptible of becoming obese, an agent which increases the  
amount of eIF-4E available for a formation of eIF-4F preinitiation complex.

Claim 33 (withdrawn): The method of claim 32, wherein said agent is an agent which  
desequesters eIF-4E from 4E-BP1.

Claim 34 (withdrawn): A method of determining whether an agent modulates obesity  
in an animal comprising:

- a) providing a translationally active preparation of translation factors and  
at least one mRNA having a cap structure whose translation is cap-dependent;
- b) measuring the initiation of translation on said mRNA, or the binding of  
at least some translation factors of a) to said cap of said mRNA in the presence and in the  
absence of an agent suspected of modulating the translation efficiency of cap-dependent  
mRNAs or the binding of translation factors to the cap structure thereof, thereby identifying  
an agent which modulates cap-dependent translation and wherein a difference in the  
translation activity and/or binding in the presence of the agent, as compared to that in the  
absence thereof identifies said agent as a modulator of cap-dependent translation;

c) administering said agent identified in b) to an animal; and  
d) assessing obesity in the animal of step c) and comparing same with that of a control animal, not having been administered said agent, wherein a difference in obesity of the animal of step c) as compared to that of the control animal identifies said agent as a modulator of obesity *in vivo*.

Claim 35 (withdrawn): The method of claim 18, where the agent is obtained from a library of compounds.

Claim 36 (withdrawn): The method of claim 35, wherein the animal is a mammal.

Claim 37 (withdrawn): The method of claim 36, wherein said mammal is a mouse or human.

Claim 38 (withdrawn): A modulator of glucose and/or fat metabolism *in vivo* identified by the method of claim 7.

Claim 39 (withdrawn): A method of treating diabetes type II and associated complications, comprising administering to an animal suffering from type II diabetes, or at risk of suffering therefrom, an agent which increases the amount of eIF-4E available for a formation of eIF-4F preinitiation complex.

Claim 40 (withdrawn): The method of claim 39, wherein said agent is an agent which desequesters eIF-4E from 4E-BP1.

Claim 41 (withdrawn): A method of identifying an agent which modulates glucose and/or fat metabolism *in vivo* comprising:

- a) incubating a portion of eIF-4E capable of directly binding with a peptide comprising an eIF-4E-binding domain;
- b) assessing said direct binding between said portion of eIF-4E and said peptide in a presence and in an absence of an agent wherein an agent which potentially modulates glucose and/or fat metabolism is identified when a difference in said binding in the presence of said agent, as compared to that in the absence thereof is observed;
- c) administering said agent identified in b) to an animal; and
- d) measuring glucose and/or lipid levels in the animal of step c) and comparing same with that of a control animal, not having been administered said agent,

wherein a difference in glucose and/or lipid levels of the animal of step c) as compared to that of the control animal identifies said agent as a modulator of glucose or fat metabolism *in vivo*.